



**Pediatric Focused Safety Review:
Cymbalta[®] (duloxetine)
Pediatric Advisory Committee Meeting
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Outline

- Background Information
- Pediatric Studies
- Labeling Changes
- Drug Use Trends
- Safety
- Summary

Background Drug Information

Cymbalta[®](duloxetine)

- **Drug:** Cymbalta[®]
- **Formulations:** delayed-release capsules, oral
- **Sponsor:** Lilly
- **Original Market Approval:** August 3, 2004
- **Therapeutic Category:** Serotonin and norepinephrine reuptake inhibitor

Background Drug Information, continued

Cymbalta[®](duloxetine)

Indications:

- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)
- Diabetic Peripheral Neuropathic Pain
- Fibromyalgia
- Chronic Musculoskeletal Pain

Only generalized anxiety disorder is approved in pediatric patients ages 7-17 years. Approved October 16, 2014

Pediatric Studies

Cymbalta[®](duloxetine)

- Major Depressive Disorder – Two 10 week placebo-controlled trials in 800 patients age 7-17 years. Efficacy was not demonstrated.
- Generalized Anxiety Disorder – One 10 week, placebo-controlled trial in 272 patients age 7 to 17 years. Cymbalta[®] demonstrated superiority over placebo as measured by greater improvement in the Pediatric Anxiety Rating Scale for GAD severity score.

Pediatric Labeling Change

Cymbalta[®] (duloxetine)

2 DOSAGE AND ADMINISTRATION

2.2 Dosage for treatment of Generalized Anxiety Disorder

Children and Adolescents (7 to 17 years of age) -Initiate Cymbalta[®] at a dose of 30 mg once daily for 2 weeks before considering an increase to 60 mg. The recommended dose range is 30 to 60 mg once daily.

6 ADVERSE REACTIONS

6.1 Clinical Trial Data Sources

Children and Adolescents – Data reflect exposure to Cymbalta[®] in 10 week placebo-controlled trials for MDD (N=341) and GAD (N=135). Patients received 30-120 mg per day. Additional data come from the overall total of 822 pediatric patients exposed to Cymbalta[®] in clinical trials up to 36 weeks in length in which most patients received 30-120 mg per day.

Pediatric Labeling Change, continued

Cymbalta[®] (duloxetine)

6 ADVERSE REACTIONS

6.11 Adverse Reactions Observed in Children and Adolescent Placebo-Controlled Clinical Trials

- The adverse drug reaction profile observed in pediatric clinical trials (children and adolescents) was consistent with the adverse drug reaction profile observed in adult clinical trials.
- The most common ($\geq 5\%$ and twice placebo) adverse reactions observed in pediatric clinical trials include: nausea, diarrhea, decreased weight, and dizziness.

Pediatric Labeling Change, continued

Cymbalta[®] (duloxetine)

Treatment-Emergent Adverse Reactions: Incidence of 2% or More and Greater than Placebo in three 10-week Pediatric Placebo-Controlled Trials^a

System Organ Class/Adverse Reaction	Percentage of Pediatric Patients Reporting Reaction	
	CYMBALTA (N=476)	Placebo (N=362)
Gastrointestinal Disorders		
Nausea	18	8
Abdominal Pain ^b	13	10
Vomiting	9	4
Diarrhea	6	3
Dry Mouth	2	1
General Disorders and Administration Site Conditions		
Fatigue ^c	7	5
Investigations		
Decreased Weight ^d	14	6
Metabolism and Nutrition Disorders		
Decreased Appetite	10	5
Nervous System Disorders		
Headache	18	13
Somnolence ^e	11	6
Dizziness	8	4
Psychiatric Disorders		
Insomnia ^f	7	4
Respiratory, Thoracic, and Mediastinal Disorders		
Oropharyngeal Pain	4	2
Cough	3	1

^a The inclusion of an event in the table is determined based on the percentages before rounding; however, the percentages displayed in the table are rounded to the nearest integer.

^b Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain.

^c Also includes asthenia.

^d Frequency based on weight measurement meeting potentially clinically significant threshold of $\geq 3.5\%$ weight loss (N=467 CYMBALTA; N=354 Placebo).

^e Also includes hypersomnia and sedation.

^f Also includes initial insomnia, insomnia, middle insomnia, and terminal insomnia.

Pediatric Labeling Change, continued

Cymbalta[®] (duloxetine)

6 ADVERSE REACTIONS

6.11 Adverse Reactions Observed in Children and Adolescent Placebo-Controlled Clinical Trials, continued

- Other adverse reactions that occurred at an incidence of less than 2%, but were reported by more Cymbalta[®] treated patients than placebo treated patients and are associated with Cymbalta[®] treatment: abnormal dreams (including nightmare), anxiety, flushing (including hot flush), hyperhidrosis, palpitations, pulse increased, and tremor.
- The most commonly reported symptoms following discontinuation of Cymbalta[®] in pediatric clinical trials have included headache, dizziness, insomnia, and abdominal pain
- Growth (Height and Weight) – Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs.

Pediatric Labeling Change, continued

Cymbalta[®] (duloxetine)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Generalized Anxiety Disorder – Efficacy was demonstrated in one 10-week, placebo-controlled trial in 272 patients age 7 to 17 years. Cymbalta[®] demonstrated superiority over placebo as measured by greater improvement in the Pediatric Anxiety Rating Scale for GAD severity score. The safety and effectiveness in pediatric patients less than 7 years of age have not been established.

Major Depressive Disorder – Efficacy was not demonstrated in two 10-week, placebo-controlled trials with 800 pediatric patients with MDD, age 7-17.

The most frequently observed adverse reactions in the clinical trials included nausea, headache, decreased weight, and abdominal pain. Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Perform regular monitoring of weight and growth in children and adolescents treated with an SNRI such as Cymbalta[®].

Pediatric Labeling Change, continued

Cymbalta[®] (duloxetine)

14 Clinical Studies

14.2 Generalized Anxiety Disorder – Includes a description of the study design, the results of the primary efficacy measure (change from baseline in the Pediatric Anxiety Rating Scale for GAD severity score).



Pediatric Drug Utilization: Cymbalta® (duloxetine)

Nationally estimated number of patients receiving dispensed prescriptions for Cymbalta® (duloxetine) by patient age* from U.S. outpatient retail pharmacies²

	August 2013 - September 2014	
	# of Patients	% Share
Total Patients	3,281,503	100.0%
0-16 years	14,445	0.4%
0-1 years	92	0.6%
2-5 years	116	0.8%
6-11 years	790	5.5%
12- 16 years	13,582	94.0%
17+ years	3,268,427	99.6%
Unknown Age	4,682	0.1%

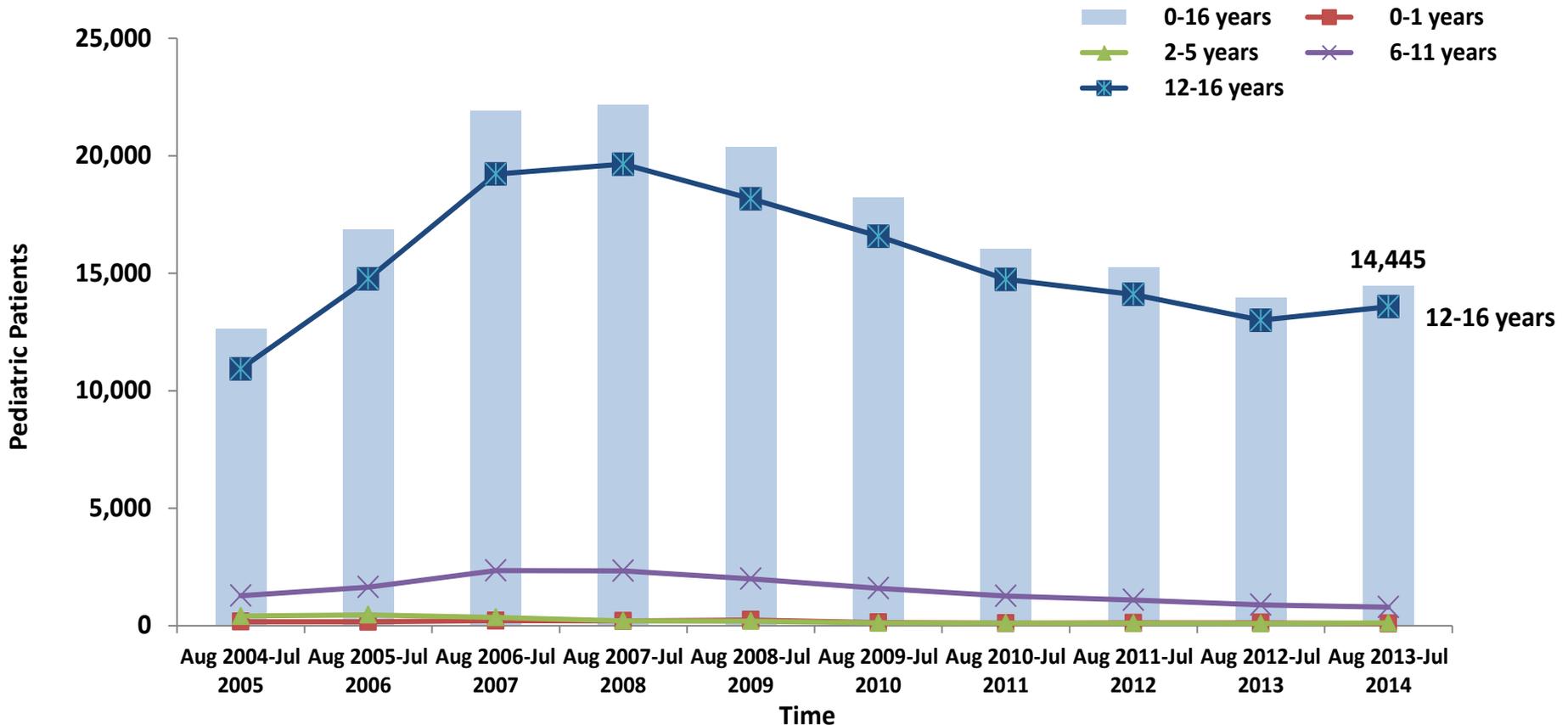
*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

**Summing patients across patient age bands will result in double counting and overestimates of patient counts.

²Source: IMS Health, Vector One®: Total Patient Tracker. August 2009 through July 2014. Data extracted November 2014.

Pediatric Drug Utilization: Cymbalta® (duloxetine)¹

Nationally estimated number of *pediatric patients (0-16 years)* receiving dispensed prescriptions for Cymbalta® (duloxetine) by patient age* from U.S. outpatient retail pharmacies



¹Source: IMS Health, Vector One®: Total Patient Tracker. August 2004 through July 2014. Data extracted December 2014.

Drug Utilization Data

- **Top Prescribing Specialties³**
(% of total outpatient retail prescriptions dispensed)
 - Family Practice (22%)
 - Pediatric specialists accounted for <1% of all prescriptions

- **Top Diagnoses as Captured in Office-Based Physician Survey⁴:**
 - 2-5 years: Myalgia and Myositis NOS*
 - 6-11 years: Depressive Psychology, Single Episode
 - 12-16 years: Depressive Disorder NEC*
 - No diagnosis data were captured for patients 0-1 year

*NOS– Not otherwise specified, NEC– Not elsewhere classified

³IMS Health, National Prescription Audit. August 2009 through July 2014. Data extracted November 2014.

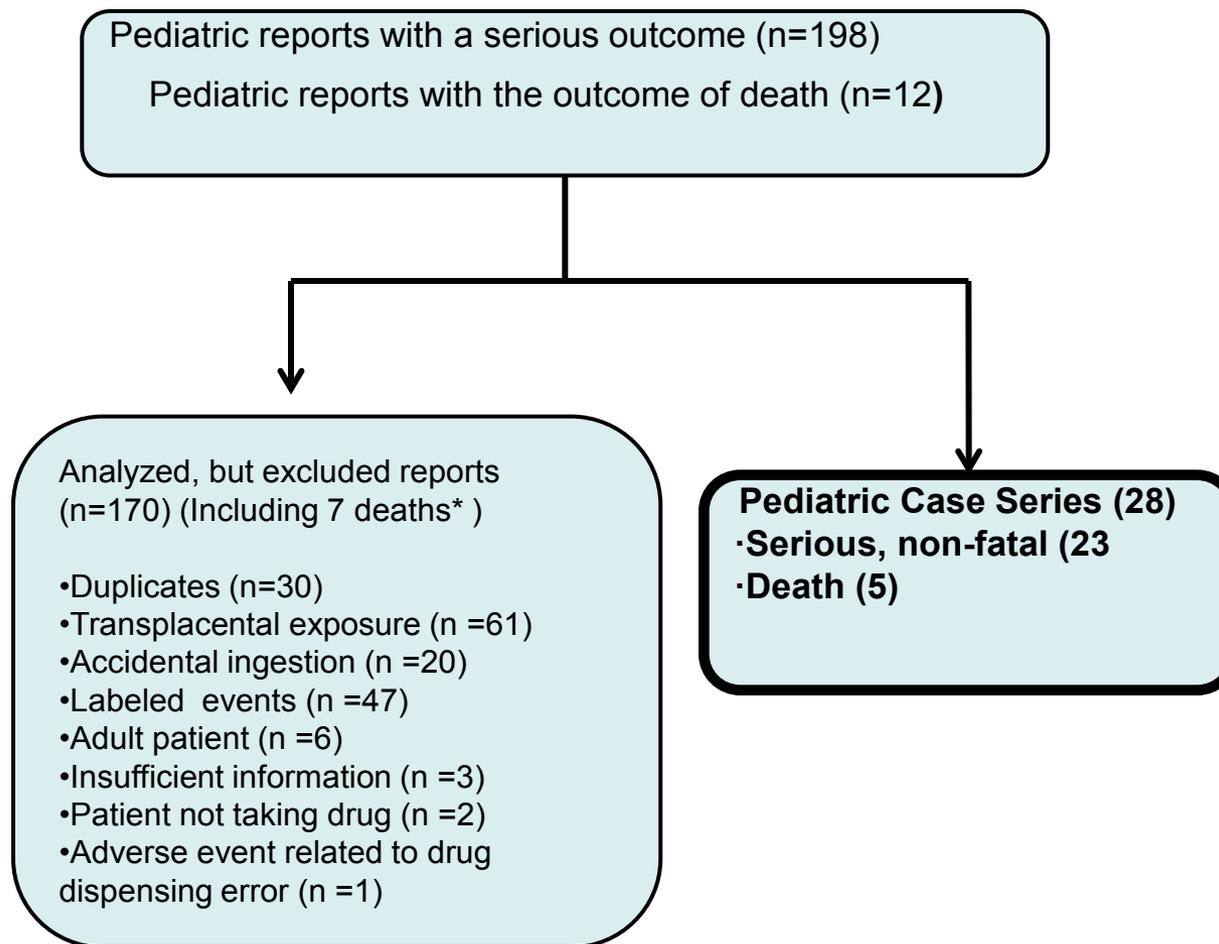
⁴Encuity Research, LLC, Treatment Answers (TM). August 2004 - July 2014 Extracted October 2014.

Number* of Adult and Pediatric Duloxetine Cases in the FDA Adverse Event Reporting System (FAERS) Since Approval August 3, 2004 to July 31, 2014

	All reports (US)	Serious [†] (US)	Deaths [§] (US)
Adults (≥ 17 yrs.)	17,763 (12,854)	12,607 (8,116)	1,787 (1,348)
Pediatrics (0- <17 yrs.)	244(164)	198 (121)	12 (10)

* May include duplicates and transplacental exposures; cases have not been assessed for causality
[†]Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events
[§] Does not include null age death reports

Selection of Pediatric FAERS Cases



*One death was excluded because the patient did not take the drug. Three deaths were excluded because the patient was exposed in-utero. The remaining deaths were duplicate reports.

Fatal Pediatric Cases (n=5)

Cymbalta[®] (duloxetine)

- A 16 year old male committed suicide by gunshot. He was taking duloxetine for two months for panic disorder. He was also taking rizatriptan. He had a history of depression, suicidal ideation, attention deficit hyperactivity disorder and drug and alcohol use.
- A 16 year old female committed suicide by unknown means. She was taking 150 mg of Wellbutrin for 5 days and an unknown dose of duloxetine for an unknown period of time at the time of her death.
- A 15 year old female with a history of depression on duloxetine for 1 year committed suicide by strangulation. Concomitant medications included dicyclomine and one to two weeks of modafinil.

Fatal Pediatric Cases, continued

Cymbalta[®] (duloxetine)

- A 16 year old male committed suicide by gunshot. Concomitant medication included zaleplon. The patient had a history of depression, asthma, myopia and congenital club foot. The death occurred approximately one month after starting duloxetine, but it is unknown per the reporter if he was taking duloxetine up until the time of death.
- An eight year old male died of “acute intoxication from a mix of paracetamol and prescription drugs which included an unspecified painkiller, an unspecified muscle relaxant, and unspecified anti-psychotic medication and duloxetine.” The case stated the patient was a victim of a crime “having been snatched off the street.”

Serious Non-Fatal Unlabeled Adverse Events **Cymbalta[®] (duloxetine)(n=23)**

Psychiatric Disorders (n=7)

Nervous System Disorders
(n=5)

Infections and Infestations
(n=3)

Eye Disorders (n=2)

Investigations (n=2)

Cardiac Disorders (n=1)

Injury, Poisoning and
Procedural Complications
(n=1)

Renal and Urinary Disorders
(n=1)

Hepatobiliary Disorders
(n=1)

Serious Non-Fatal Unlabeled Adverse Events, continued, Cymbalta[®] (duloxetine)

Psychiatric Disorders (n=7)

Psychotic Disorders (n=3)

- A 15 year old female taking duloxetine for fibromyalgia experienced worsening of depression, nausea, vomiting, psychotic disorder (psychosis) and tremor at an unknown time following initiation of duloxetine. She was hospitalized. Past medical history included adjustment disorder and Asperger Syndrome and concomitant medications of amitriptyline and pregabalin. Duloxetine was discontinued and patient improved.
- 15 year old male taking duloxetine for depression was reported to be manic and aggressive 10 days after starting duloxetine. Duloxetine was discontinued. Following discontinuation, the patient developed a psychotic state and was hospitalized. At the time of the report, the patient had not recovered.
- 10 year old male receiving 90 mg daily duloxetine. The patient was brought to the ER because he was suicidal and out of control. He had disorganized thoughts and speech, delusions and vocal hallucinations. He was hospitalized for an acute psychotic disorder. Duloxetine was discontinued and the patient recovered.

Serious Non-Fatal Unlabeled Adverse Events, continued, Cymbalta[®] (duloxetine)

Psychiatric Disorders, continued

Homicide (n=1)

- 15 year old male received duloxetine for depression after attempted suicide. Over next two week, patient developed “hypomania with agitation, psychic activation, periods of euphoria, pressure of speech, worsening insomnia and akathisia.” The patient committed a double murder and on the same day tried to shoot himself. He was arrested and hospitalized.

Self-Injurious Behavior (n=1)

- 15 year old female stabbed herself in the thigh and attempted to stab her mother after taking prescribed meds to control leg pain. She was admitted to a mental health facility.

Obsessive-Compulsive Disorder/Crying/Negative Thoughts (n=1)

- 15 year old female taking duloxetine (30 mg daily) for pain began exhibiting obsessive-compulsive behavior. The patient was taken to the hospital with worsening anxieties and bad thoughts. She was trembling and crying uncontrollably. She was admitted and duloxetine was discontinued. The patient was starting to do better at the time of the report.

Serious Non-Fatal Unlabeled Adverse Events, continued, Cymbalta[®] (duloxetine)

Psychiatric Disorders, continued

Tics/Urinary Tract Infection/Conversion Disorder/Dysphemia (n=1)

- 16 year old female was on duloxetine 20 mg TID for functional abdominal pain. Duloxetine was increase to 60 mg daily over 2 weeks. After the first dose increase, the patient experienced twitching in one leg and a urinary tract infection. After the second dose increase, the patient experienced a “brief episode of trembling of the arms, legs, and neck as well as tics in the head and neck” and stuttering. The patient was hospitalized and duloxetine was discontinued. At the time of the report, the patient had recovered from all symptoms except the tremors, twitching and tics.

Serious Non-Fatal Unlabeled Adverse Events, continued, Cymbalta[®] (duloxetine)

Nervous System Disorders: (n=5)

Loss of consciousness (n=3)

- A 15 year old was on 60 mg of duloxetine for depression. The dose was decreased to 30 mg after the patient “felt weird.” He experienced progressive mood swings and a few days later became unresponsive at school. He was taken to the ER, but not admitted. Duloxetine was discontinued.
- A 14 year old female missed 3 doses of duloxetine became lethargic and was non-responsive. She was seen, but not admitted to the hospital. Duloxetine was continued at a decreased dose. The patient continued to have lethargy.
- A 15 year old with elevated blood pressure (140/110) while on duloxetine lost consciousness four times. She experience urinary incontinence twice while unconscious. She was taken to the ER and duloxetine was discontinued. The patient recovered.

Serious Non-Fatal Unlabeled Adverse Events, continued, Cymbalta[®] (duloxetine)

Nervous System Disorders, continued:

Cerebrovascular Accident (n=1)

- A child began taking duloxetine (date started, dose and indication unspecified). The patient experienced a stroke. Limited available information.

Slow Response to Stimuli/Confusional State/Speech Impairment (n=1)

- A 16 year old female experienced yawning, tremors somnolence and “wobbly” legs after one or two days of duloxetine. She could listen to her mother, but could not speak. She was slow to respond to stimuli. The patient also experienced an increase in blood pressure. The report stated that she did not recover from the events.

Serious Non-Fatal Unlabeled Adverse Events, continued, Cymbalta[®] (duloxetine)

Infections and Infestations (n=3)

Appendicitis (n=1)

- 15 year old female developed urinary retention two months after starting 60 mg duloxetine. Duloxetine was discontinued and the urinary retention resolved. Later the patient underwent a laproscopic appendectomy for a mild appendicitis infection.

Chest Pain/Hypoventilation/Esophageal Pain/Pneumonia/Unresponsive to Stimuli (n=1)

- 14 year old male on 60 mg daily duloxetine for postural orthostatic hypotension experienced increase sleeping, symptoms of a cold or flu, possible pneumonia, right upper quadrant abdominal pain, chest pain, and lung pain. He experienced unresponsiveness, shallow breathing, difficulty sleeping, and irritability. He was taken to the ER and given ketorolac and meperidine. The results of the chest X-ray are unknown.

Hepatitis (n=1)

- A 12 year old female was on duloxetine 20 mg daily for depression. She had traveled to Costa Rica for two weeks. She was nauseous after initiating duloxetine and four or five days later she developed yellow eyes and dark urine. She was diagnosed with Hepatitis A. The dose of duloxetine was continued, but decreased to 20 mg every other day.

Serious Non-Fatal Unlabeled Adverse Events, continued, Cymbalta[®] (duloxetine)

Eye Disorder (n=2)

Eye disorder/dilated pupils (n=1)

- A 14 year old female was given 60 mg daily duloxetine for the treatment of “sadness”. One hour after taking the first dose she “felt bad” and was hospitalized with symptoms of shakiness, purple eyes, dilated pupils and dizziness. Duloxetine was discontinued. The dizziness did not resolve. It is unknown if the other symptoms resolved.

Pupils unequal (n=1)

13 year old male developed a headache and unequal pupils within 24 hours of starting duloxetine. Head CT and MRI were normal. Neurologic exam was normal. Duloxetine was discontinued and the event resolved.

Investigations (n=2):

White Blood Cell Decreased (n=1)

- A 15 year old patient experienced a decrease in leucocytes reported as “fluctuating leucocytes” approximately one month after starting duloxetine. Duloxetine was discontinued and the patient recovered. The patient had previously experienced “fluctuating leucocytes” while also being treated with fluvoxamine maleate.

Gamma-Glutamyltransferase Increased (n=1)

- A 16 year old male receiving duloxetine 20 mg for an unknown indication became jaundice after 3 months with a GGT level of 179, normal bilirubin, ALT of 61 and AST of 44. Duloxetine was discontinued. The outcome was not reported.

Serious Non-Fatal Unlabeled Adverse Events, continued, Cymbalta[®] (duloxetine)

Cardiac Disorders (n=1)

Electrocardiogram QT Corrected Interval Prolonged/Left Ventricular Systolic Dysfunction

- A 14 year old female diagnosed with acute myeloid leukemia on duloxetine and multiple concomitant medications including Bactrim, bortezomib, voriconazole and daunorubicin. The patient experienced electrocardiogram QT corrected interval prolongation and left ventricular systolic dysfunction. The patient was given milrinone in the ICU and bortezomib was discontinued. The action taken with duloxetine and the other medications was not specified. The events were resolving at the time of the report.

Injury, Poisoning and Procedural Complications (n=1)

Road traffic accident

- A 16 year old male was “run over by a car” while on duloxetine. Concomitant medications included trazodone for a sleep disorder. He was doing well on duloxetine at the time of the event.

Serious Non-Fatal Unlabeled Adverse Events, continued, Cymbalta[®] (duloxetine)

Renal and Urinary Disorders (n=1)

Incontinence

- A 16 year old female on 60 mg daily duloxetine for chronic pain syndrome became incontinent 2 months after starting duloxetine. Duloxetine was discontinued over a one week taper. After discontinuation, she began having debilitating dizziness with vomiting. She was sensitive to light and had nystagmus.

Hepatobiliary Disorders (n=1)

Hepatic Failure/Hepatotoxicity/Infectious Mononucleosis/Sedation/Asterixis/Confusion

- 16 year old male on duloxetine for an unknown indication. The patient has a history of depression, ADHD, self injury, passive suicidality, oppositional defiant disorder, and ethanol and chewing tobacco use. The patient was hospitalized with a two week history of worsening slurred speech, malaise, clumsiness, hand flapping, jaundice, dehydration, mild abdominal pain, confusion/disorientation, tremors blurry vision and tinnitus. Duloxetine was discontinued. Diagnoses upon discharge were infectious mononucleosis, medication induced liver toxicity, global cortical atrophy and ataxia.

Summary of Safety Reviews

Cymbalta[®] (duloxetine)

- This concludes the pediatric focused safety review of FAERS reports
- No potential safety signals were identified
- FDA recommends continued routine monitoring
- Does the committee concur?

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